

Normal Tension Glaucoma

Literature review

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Abstract

Normal tension glaucoma is a disease that causes glaucomatose damage to the optic nerve without the presence of elevated intraocular tensions. New studies have emerged that shine a new light on possible pathologic mechanisms and present new therapeutic approaches to this disease. We present an inclusive literature review, focusing on these new developments, comparing them with older notions and treatments, and discussing epidemiology data and diagnostic methods.

Resumo

O Glaucoma de Tensão Normal é uma patologia que provoca alterações glaucomatosas no nervo óptico sem se constatar pressões intraoculares elevadas. Têm surgido novos estudos científicos que lançam um novo olhar sobre os possíveis mecanismos fisiopatológicos e apresentam novas estratégias terapêuticas para esta doença. Apresentamos uma revisão da literatura inclusiva, abordando estas novas noções, comparando-as com postulados e tratamentos anteriores, e discutindo dados epidemiológicos e métodos de diagnóstico.

Introduction

In 1857, Albrecht von Graefe, a German ophthalmologist, recognised and described for the first time glaucomatous optic neuropathy in the setting of physiologic intraocular pressure (IOP). Since then, scientists and ophthalmologists have been discussing whether Normal Tension Glaucoma (NTG) is just a part of the spectrum of Primary Open-Angle Glaucoma (POAG) or an entirely different disease, with a distinct pathophysiology. Recent studies have suggested new theories on the development of this disease that may open doors to alternative therapies in the treatment of, not only NTG, but also all types of glaucoma.

Review methods and selection process

Literature was searched through the following methods:

a) Using the following keywords in the *Google Scholar* search engine: "normal tension glaucoma", "normal tension glaucoma pathophysiology", "normal tension glaucoma epidemiology", "normal tension glaucoma treatment", "normal tension glaucoma associated disorders", among others.

b) Similar papers suggestions by *Google Scholar* and *Pubmed*, according to tittle and abstract relevance.

c) Reading Ophtalmology text books (Shaarawy, Sherwood, Hitchings, & Crowston, 2015)

d) Consulting *Medscape's* webpage concerning normal tension glaucoma (Freudenthal, 2014)

The selection of the articles was made according to the study pertinence and statistic significance. Preference was given to articles published in the last 10 years, with inclusion of pertinent or historically important papers.

Epidemiology

NTG is fairly infrequent in European and American populations but is very common in Eastern Asia. A study based on an American population found that Asian Americans have a 51% increased hazard of Open-Angle Glaucoma (OAG), a 123% increased risk of developing closed-angle glaucoma and a 159% increased probability of having NTG, compared with non-Hispanic whites (Stein et al., 2011). In fact, NTG is the most common type of open-angle glaucoma in Japan: the prevalence of POAG in this population is calculated to be around 3.9%, with 92% of these patients having IOP less than 21 mmHg (Iwase et al., 2004). Similar incidences were found in a study of a selected Korean population (C. S. Kim, Seong, Lee, & Song, 2011).

Pathophysiology

NTG is a multifactorial chronic optic neuropathy that features characteristics similar to POAG, except for high IOP, the values of which are consistently under 23 mmHg (M. Kim, Kim, Park, & Kim, 2012). Diagnostic criteria can be defined as (1) the presence of open iridocorneal angles, (2) untreated IOP less than 21mmHg in multiple measures, (3) progressive changes in either visual fields or optic nerve cupping and (4) absence of other causes of optic neuropathy. (Tezel, Kass, Kolker, & Wax, 1996). The clinical appearance of the optic nerve damage, through ophthalmoscopy, is no different between POAG and NTG (Tezel et al., 1996). However, the absence of an abnormal IOP suggests dissimilar pathological development.

a) Increased susceptibility to high intraocular pressure

IOP, though within normal values, may be nevertheless important to the progression of NTG, as demonstrated by the fact that medical therapy which lowers IOP slows the progression of glaucomatose neuropathy even in NTG (Colaborative Normal-Tension Glaucoma Study Group, 1998).

IOP values in NTG are often higher than reference values for a healthy population, while still being under 21mmHg (M. Kim et al., 2012). Corneal hysteresis and corneal resistance factor are significantly lower in NTG (Grise-Dulac et al., 2011;

Morita, Shoji, Kamiya, Fujimura, & Shimizu, 2012). Since biomechanical properties of the cornea reflect those of the eyeball as a whole, there may exist an increased susceptibility to high IOP in NTG patients related to deformities in the eyeball itself.

b) Metabolic damage caused by vascular dysfunction

Other factors may be of great importance in NTG development besides IOP. In POAG, increased IOP exerts an abnormal mechanical stress on the optic nerve, leading to mechanical damage of glial astrocytes in the optical nerve head, their incapability to support the metabolism of axons and, ultimately, the death of retinal ganglion cells (Dai et al., 2012). In NTG the same damage to astrocytes may exist but due to metabolic damage rather than mechanical stress.

It has been theorized that an association between systemic vascular dysfunctions and NTG exists (Flammer, Konieczka, & Flammer, 2013). Vascular dysregulation, a term that embraces arterial spasms, and inappropriate constrictions and dilatations of arteries, veins or capillaries, can affect any organ, including the eye (Flammer et al., 2013). The progression of glaucomatose visual field damage in POAG correlates with altered retrobulbar hemodynamic variables, such as low baseline blood flow velocities and high baseline resistivity in the central retinal artery (Satilmis, Orgül, Doubler, & Flammer, 2003). When comparing nocturnal systemic blood pressure variability, peripheral arterial stiffness, carotid intima-media thickness, and ocular perfusion pressure between POAG patients, NTG patients and healthy controls, one reaches the conclusion that patients with POAG or NTG exhibit similar changes in ocular and systemic circulation in the early stages of their disease process, which are not present in controls (Mroczkowska, 2012). Also, early stage, newly diagnosed, NTG patients showed signs of sub-clinical vascular abnormalities at both macro and microvascular levels (Mroczkowska et al., 2012). Another study found NTG patients exhibited a shift towards sympathetic activity when several variables related to sympathovagal balance were analysed. Such imbalance may result in increased vascular resistance and may have circulatory implications (Wierzbowska, Wierzbowski, Stankiewicz, Siesky, & Harris, 2012). Nocturnal blood pressure dipping and greater variation of ocular perfusion pressure were as well found in NTG patients (Choi et al., 2013; Ramli, Nurull, Hairi, & Mimiwati, 2013). All these studies

suggest that some degree of ischemia in the optic nerve has importance in NTG (and to some degree, POAG) pathophysiology.

Obstructive sleep apnea syndrome is a disease characterized by repetitive upper airway obstructions during sleep, inducing hypoxia and sleep disruption. There is a high prevalence of sleep apnea syndrome in normal-tension glaucoma patients. (Bilgin, 2014; Mojon et al., 2002). The direct pathological link between sleep apnea syndrome and NTG is not yet established, but one can hypothesise that the disease causes glaucomatous damage to the optic nerve by means of hypoxia and vascular dysregulation (Gutiérrez-Díaz, Pérez-Rico, de Atauri, Mencía-Gutiérrez, & Blanco, 2012; Lin et al., 2011)

c) Metabolic damage caused by autoimmunity

There is also scientific evidence that favours a role for autoimmunity in glaucoma development. Many molecules overexpressed in autoimmune diseases are also raised in glaucoma (POAG and NTG) patients, such as TNF-alpha, matrix metalloproteinases, interleukin 6 and others (Wax, 2011). However, despite this evidence, it is still difficult to establish a clear pathophysiologic link between these measurements and glaucoma, though it can be theorised that, if autoimmunity has a role in glaucoma, it may be responsible for initiating a cascade of events similar to those that happen with vascular injury.

In short, vascular dysfunction as well as autonomic dysfunction can lead to a poor blood perfusion to the ocular tissues, including the optic nerve. This, as with autoimmunity, may cause a rise in oxidative stress and a subsequent release of inflammation mediators, activation of astrocytes, a raise of glutamate levels and damage to retinal ganglion cells.

Diagnostic procedures and workup

The diagnosis of NTG is made when optic disc cupping and glaucomatous visual field defects are found in conjunction with normal IOP. (Sheleg, 2011). However, other pathologies should be excluded. Therefore, some diagnostic procedures are necessary.

a) History

Careful history should be taken. The ophthalmologist should inquire about episodes of ocular pain, which may indicate previous acute angle closure attack, and other probable causes of optic nerve damage, such as trauma, uveitis and steroid treatment. The use of systemic medication that lowers IOP, as beta-blocker, should be assessed. Glaucomatous damage in spite of low IOP measurements may result from low compliance, in patients that only take anti-glaucoma medications before their medical examinations.

Blood pressure, ischemic vascular disease, perfusion pressure, vasospastic disorders (migraine, Raynaud phenomenon) and obstructive sleep apnea are conditions associated with NTG and should therefore be assessed in selected cases.

b) Ophthalmologic exam

To begin with, ocular hypertension as well as POAG must be excluded, by measurement of IOP. A diurnal curve of IOP should be performed. IOP values should be inferior to 21 mmHg throughout the day.

The anterior chamber should be analysed. NTG has an open, normal appearing angle. Angle closure and angle recession should therefore be excluded.

Corneal thickness is thinner in NTG (Copt, Thomas, & Mermoud, 1999) and can be measured by ultrassound pachymetry. Pachymetry is also useful to adjust the difference between measured IOP by Goldman tonometry and true IOP (Morita et al., 2010). Keratic precipitates point to a uveitis diagnosis and Krukenberg spindle indicate pigment dispersion.

Glaucomflecken in the lens point to previous IOP elevation, usually secondary to acute angle closure. If present, NTG is excluded.

Refractive errors should be measured and considered as well.

Ocular fundus in NTG is grossly similar to POAG. However, some authors describe differences in disc optic appearance, such as greater thinning of neuroretinal rim of the disc was found in NTG (Caprioli & Spaeth, 1985). Optic disc haemorrhages can be found in both NTG and POAG patients, are very rarely found in healthy eyes (Bengtsson, 1990) and are a risk factor for progression of visual field defects in NTG (Drance, Anderson, & Schulzer, 2001). Disc haemorrhages are usually splinter or flame-shaped hemorrhages perpendicular to the optic disc border.

c) Blood tests

Erythrocyte sedimentation rate (ESR) is a useful tool in cases of decreased central acuity with a pale nerve to rule out anterior ischemic optic neuropathy (AION).

Syphilis can cause glaucomatous features. As such, rapid plasma reagent (RPR) and fluorescein treponema antibody (FTA) should be ordered to rule out ocular syphilis.

Given the connection between NTG and autoimmune diseases, it is recommended to rule them out by testing for the presence of antinuclear antibodies (ANA).

d) Complementary diagnostic exams

Optical coherence topography (OCT) is a helpful exam in the diagnosis and monitoring of glaucomatous optic neuropathy. Optic nerve head and retinal nerve fiber should be analysed.

When visual-field defects first present, especially when a marked asymmetry is present, or there is a rapid progression of neuropathy, a referral to a neurophthalmologist and magnetic resonance imaging are to be considered.

Carotid Doppler testing is recommended in patients with suspected atherosclerosis to rule out carotid insufficiency.

A 24-hour blood pressure monitoring is also recommended, given the association of NTG with nocturnal hypotension.

Treatment

The fact that IOP, even within normal statistical values may be a contributing factor to optic nerve damage has led ophthalmologists to treating NTG as one does in POAG, i.e. by lowering IOP, through medical and surgical methods.

a) Pharmacological control of IOP

Since the 1998 study by the Collaborative Normal-Tension Glaucoma Study Group, the accepted goal for NTG medical treatment has been to lower IOP by 30%

(Colaborative Normal-Tension Glaucoma Study Group, 1998). Recent literature is revising this idea, adding that lowering IOP just by 10,6% has a significant effect in stopping nerve damage progression and that the most important goal is to maintain stable IOP values (Komori, Ishida, & Yamamoto, 2014). Latanoprost, bimatoprost, timolol and brimonidine are the most effective drugs when considering the percentage of IOP reduced in NTG patients (Cheng, Cai, & Wei, 2009). Brimonidine in particular lowers IOP as effectively as timolol but has demonstrated better results as far as preserving visual field (Krupin, Liebmann, Greenfield, Ritch, & Gardiner, 2011). This is related to the fact that brimonidine improves vascular regulation in NTG (Feke et al., 2014).

b) Surgical control of IOP

Surgical procedures have been used in POAG as an alternative to pharmacological therapies in order to lower IOP. There is a small amount of studies focusing on their use in NTG.

Use of Argon Laser trabeculoplasty (ALT) in NTG resulted in IOP reductions lasting up to 21.6 months. However, ALT caused scarring that prevented repeating the procedure once the laser effect worn off. (Schwartz AL, Perman KI, 1984)

Selective Laser Trabeculoplasty (SLT) has been the focus of newer studies regarding NTG. It has been shown that it reduces mean intraocular pressure as well as intraocular pressure variation (El Mallah, Walsh, Stinnett, & Asrani, 2010). A recent study demonstrated that the effect persists at least until years after the surgery, with an average of 12% of treated eyes showing IOP reduction, with 41% fewer medication, whereas 11% of treated eyes were medication free (Lee, Shum, Chan, & Lai, 2015). Further research is needed concerning this treatment option, especially related to the way surgical procedures impact on the progression of the disease.

c) New therapies

Recently, new approaches to NTG treatment have been suggested.

Some authors argue that increasing ocular perfusion pressure (OPP) may have a positive effect in NTG. For one, anti-hypertensive treatment in patients with systemic hypertension should be reduced in order to prevent very low OPPs (Cherecheanu, Garhofer, Schmidl, Werkmeister, & Schmetterer, 2013). Second,

pharmaceutical therapy to raise OPP should be considered. An increase in daily salt consumption or fludrocortisone therapy have been suggested in order to raise systemic blood pressure and reduce nocturnal blood pressure dipping (Mozaffarieh & Flammer, 2007, 2013). This doesn't seem to be a viable option considering the comorbidities associated with high systemic blood pressure such as stroke, myocardial infarction, vascular disease, and chronic kidney disease. As stated above, brimonidine may have a role in regulating local vascular flow (Feke et al., 2014). Similarly, nifedipine, as a calcium-channel blocker, has been suggested in order to improve ocular blood flow (Harris, Evans, Cantor, & Martin, 1997).

Many authors have proposed *Ginkgo biloba* as a new neuroprotective therapy. Pharmacologically, *Ginkgo biloba* targets the factors involved in glaucomatous disease (disturbed ocular microcirculation, oxidative stress, impairment of mitochondrial function in the retinal ganglion cells): *Ginkgo biloba* has antioxidative effects, stabilizes the mitochondria, has anti-inflammatory effects, regulates microcirculation and has antithrombotic, vasorelaxative and antivasospastic properties. Therefore, theoretically, *Ginkgo biloba* could be beneficial for glaucoma (Cybulska-Heinrich, Mozaffarieh, & Flammer, 2012; Shim, Kim, Choi, Kim, & Park, 2012). It has been used recently by clinicians as adjuvant therapy for NTG, in addition to tension-lowering drugs (Cybulska-Heinrich et al., 2012; Mozaffarieh & Flammer, 2007).

d) The future of NTG therapy

Murine models of NTG have been used to test the neuroprotective effects of known neurologic active drugs. Valproic acid, for instances, was shown to suppress retinal degradation, ameliorate deterioration in visual function, reduce the oxidative stress level and stimulate retinal cell survival signalling in mice with deletion of glutamate transporter genes glutamate/aspartate transporter (GLAST KO), a murine model for normal tension glaucoma (Kimura et al., 2015). This means that a commonly used drug with known safety profiles, such as valproic acid may be of interest as a treatment for NTG.

New molecules have also been tested on murine models. Dock3 (Dedicator of cytokinesis 3) is a molecule found to promote axon regeneration following optic nerve injury. Dock3 overexpression prevents glaucomatous retinal degeneration by

suppressing both NR2B-mediated glutamate neurotoxicity and oxidative stress in GLAST KO mice. Dock3 signalling pathway comes across as a potential therapeutic target for both neuroprotection and axonal regeneration in glaucoma (Namekata et al., 2013).

Conclusion

There is still much to be understood concerning the topic of NTG. Further investigation is necessary regarding the physiopathological mechanisms behind this ophthalmic disease.

Some questions still remain. What explains the difference in incidence between Japan and Korea and western countries? Is NTG under-diagnosed in Europe and America? Should glaucomatous damage be searched for in patients with sleep apnea or migraines? What about in patients with autoimmune diseases?

What seems certain is that new treatments that may arise from investigation in NTG patients may present as further therapeutic options in patients with other types of glaucoma, as new studies are focusing on the approach to the damage in the optic nerve itself.

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